NTP Research Concept: *o*-Phthalaldehyde

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Nomination Background and Rationale
o-Phthalaldehyde (OPA) was nominated by the National Institute for Occupational Safety and Health for toxicological characterization based on the limited availability of toxicological data and its increasing use as an alternative to glutaraldehyde in the disinfection of heat sensitive dental and medical equipment (http://ntp.niehs.nih.gov/go/29287). OPA has been approved by the U.S. FDA for disinfecting medical devices and is marketed, sold, and used as a "safe" replacement for glutaraldehyde. Glutaraldehyde is a strong skin, eye, and respiratory irritant and has been demonstrated to cause sensitization and occupational asthma in humans. The compounds differ in molecular structure in that glutaraldehyde is a straight-chained hydrocarbon, whereas OPA is a benzene ring based structure. The safety of OPA relative to glutaraldehyde is largely based on its greater efficacy as a disinfectant, which allows for use at lower concentrations. There is no specific data or information indicating that OPA is a safe alternative to glutaraldehyde and neither OSHA nor the U.S. EPA have promulgated rules regarding safe exposure levels. There are virtually no peer-reviewed toxicological data in the open literature for OPA. Both the U.S. EPA and U.S. FDA have received unpublished animal toxicity reports, which are protected as confidential business information. Based on summary information in the available Material Safety Data Sheet, statements on the internet, and general summaries of some of the confidential reports, it appears that OPA is not a developmental toxicant or mutagenic in bacterial tests, but it does induce chromosomal aberrations in mammalian cell assays and is moderately toxic in subchronic toxicological studies. While no published data are available for review, OPA has been noted as positive in the guinea pig maximization test and the mouse local lymph node assay. Consistent with this, a few human case reports indicate that OPA can cause mucous irritation, respiratory symptoms and IgE-mediated hypersensitivity reactions. These studies are limited in scope, but suggest that OPA may pose similar occupational hazards to those of glutaraldehyde. However, data are needed to define and document the potential hazard posed to healthcare workers handling OPA so that appropriate guidelines and protections can be put into place.

Key Issues
A major issue with respect to heath care worker exposure is the vapor pressure of OPA. It has been suggested that a benefit of OPA relative to glutaraldehyde is the lower required concentration and low vapor pressure of OPA. There are no published studies available for OPA vapor pressure. Vapor pressure of OPA will need to be determined in solutions appropriate for use in toxicology studies and in selected commercial products. The measurement of vapor pressure and input from NIOSH regarding their specific data needs will be used to determine appropriate routes of exposure for subchronic toxicity studies. Prior NTP subchronic and chronic inhalation studies of glutaraldehyde will be used to allow comparisons between OPA and glutaraldehyde. However, additional glutaraldehyde studies may also be required.

Proposed Approach

The overall goal of this research project is to investigate the hypothesis that OPA is a "safe" alternative to glutaraldehyde by characterizing the potential for OPA to cause dermal and respiratory sensitization and systemic toxicity. The specific aims of the proposed studies are to:

- Assess dermal irritation and sensitization
- Evaluate respiratory sensitization and asthmagenic potential
- Evaluate dermal toxicity following subchronic exposure
- Obtain ADME data

The studies to assess irritation, sensitization, and asthmagenic potential are considered high priority studies within the framework of this research program for OPA and will include studies such as the mouse local lymph node assay and the mouse ear-swelling test. The subchronic dermal toxicity and ADME studies are considered secondary priority to the other proposed studies. Continued coordination with NIOSH will be required to determine the need and priority of these and any additional studies.

The OPA product typically used in health care settings is a solution containing a concentration of 0.56% OPA. An OPA concentrate is also available on the market containing 5.75% OPA. Test material concentrations for the proposed studies will likely be limited by OPA solubility, but doses should include these commercially available concentrations.

Significance and Expected Outcome

The use of OPA in health care settings is widespread and apparently increasing. It is reasonable to assume that more than 300,000 healthcare workers may be exposed to OPA. No other exposure information (including limits) is available. According to published literature and adverse event reports submitted to the FDA, healthcare workers have experienced irritation of the eyes, skin, and nose and several patients have experienced anaphylaxis following procedures in which OPA was used to disinfect medical equipment. Although OPA has been suggested as a safer alternative to glutaraldehyde, there is an overwhelming lack of publicly available data on the safety of OPA. Based on information known regarding other aldehydes, including glutaraldehyde, there is a strong potential that *o*-phthalaldehyde may be a skin and respiratory sensitizer that may cause dermatitis with prolonged or repeated contact and may aggravate pre-existing bronchitis or asthma. The data generated from this research program will complement NIOSH's proposed studies to measure exposures to OPA in the workplace and greatly contribute to the assessment of potential health risks for healthcare workers exposed to OPA. Together these data will provide the basis for the determination of safe exposure limits for OPA and the development of guidance for protection of health care workers using OPA.